Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel

Günthard, Huldrych F ; Saag, Michael S ; Benson, Constance A ; del Rio, Carlos ; Eron, Joseph J ; Gallant, Joel E ; Hoy, Jennifer F ; Mugavero, Michael J ; Sax, Paul E ; Thompson, Melanie A ; Gandhi, Rajesh T ; Landovitz, Raphael J ; Smith, Davey M ; Jacobsen, Donna M ; Volberding, Paul A

Abstract: IMPORTANCE New data and therapeutic options warrant updated recommendations for the use of antiretroviral drugs (ARVs) to treat or to prevent HIV infection in adults. OBJECTIVE To provide updated recommendations for the use of antiretroviral therapy in adults (aged 18 years) with established HIV infection, including when to start treatment, initial regimens, and changing regimens, along with recommendations for using ARVs for preventing HIV among those at risk, including preexposure and postexposure prophylaxis. EVIDENCE REVIEW A panel of experts in HIV research and patient care convened by the International Antiviral Society-USA reviewed data published in peer-reviewed journals, presented by regulatory agencies, or presented as conference abstracts at peer-reviewed scientific conferences since the 2014 report, for new data or evidence that would change previous recommendations or their ratings. Comprehensive literature searches were conducted in the PubMed and EMBASE databases through April 2016. Recommendations were by consensus, and each recommendation was rated by strength and quality of the evidence. FINDINGS Newer data support the widely accepted recommendation that antiretroviral therapy should be started in all individuals with HIV infection with detectable viremia regardless of CD4 cell count. Recommended optimal initial regimens for most patients are 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (InSTI). Other effective regimens include nonnucleoside reverse transcriptase inhibitors or boosted protease inhibitors with 2 NRTIs. Recommendations for special populations and in the settings of opportunistic infections and concomitant conditions are provided. Reasons for switching therapy include convenience, tolerability, simplification, anticipation of potential new drug interactions, pregnancy or plans for pregnancy, elimination of food restrictions, virologic failure, or drug toxicities. Laboratory assessments are recommended before treatment, and monitoring during treatment is recommended to assess response, adverse effects, and adherence. Approaches are recommended to improve linkage to and retention in care are provided. Daily tenofovir disoproxil fumarate/emtricitabine is recommended for use as preexposure prophylaxis to prevent HIV infection in persons at high risk. When indicated, postexposure prophylaxis should be started as soon as possible after exposure. CONCLUSIONS AND RELEVANCE Antiretroviral agents remain the cornerstone of HIV treatment and prevention. All HIV-infected individuals with detectable plasma virus should receive treatment with recommended initial regimens consisting of an InSTI plus 2 NRTIs. Preexposure prophylaxis should be considered as part of an HIV prevention strategy for at-risk individuals. When used effectively, currently available ARVs can sustain HIV suppression and can prevent new HIV infection. With these treatment regimens, survival rates among HIV-infected adults who are retained in care can approach those of uninfected adults.

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Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults

2016 Recommendations of the International Antiviral Society–USA Panel

Huldrych F. Günthard, MD; Michael S. Saag, MD; Constance A. Benson, MD; Carlos del Rio, MD; Joseph J. Eron, MD; Joel E. Gallant, MD, MPH; Jennifer F. Hoy, MBBS, FRACP; Michael J. Mugavero, MD, MHSc; Paul E. Sax, MD; Melanie A. Thompson, MD; Rajesh T. Gandhi, MD; Raphael J. Landovitz, MD; Davey M. Smith, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

IMPORTANCE New data and therapeutic options warrant updated recommendations for the use of antiretroviral drugs (ARVs) to treat or to prevent HIV infection in adults.

OBJECTIVE To provide updated recommendations for the use of antiretroviral therapy in adults (aged ≥18 years) with established HIV infection, including when to start treatment, initial regimens, and changing regimens, along with recommendations for using ARVs for preventing HIV among those at risk, including preexposure and postexposure prophylaxis.

EVIDENCE REVIEW A panel of experts in HIV research and patient care convened by the International Antiviral Society–USA reviewed data published in peer-reviewed journals, presented by regulatory agencies, or presented as conference abstracts at peer-reviewed scientific conferences since the 2014 report, for new data or evidence that would change previous recommendations or their ratings. Comprehensive literature searches were conducted in the PubMed and EMBASE databases through April 2016. Recommendations were by consensus, and each recommendation was rated by strength and quality of the evidence.

FINDINGS Newer data support the widely accepted recommendation that antiretroviral therapy should be started in all individuals with HIV infection with detectable viremia regardless of CD4 cell count. Recommended optimal initial regimens for most patients are 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (InSTI). Other effective regimens include nonnucleoside reverse transcriptase inhibitors or boosted protease inhibitors with 2 NRTIs. Recommendations for special populations and in the settings of opportunistic infections and concomitant conditions are provided. Reasons for switching therapy include convenience, tolerability, simplification, anticipation of potential new drug interactions, pregnancy or plans for pregnancy, elimination of food restrictions, virologic failure, or drug toxicities. Laboratory assessments are recommended before treatment, and monitoring during treatment is recommended to assess response, adverse effects, and adherence. Approaches are recommended to improve linkage to and retention in care are provided. Daily tenofovir disoproxil fumarate/emtricitabine is recommended for use as preexposure prophylaxis to prevent HIV infection in persons at high risk. When indicated, postexposure prophylaxis should be started as soon as possible after exposure.

CONCLUSIONS AND RELEVANCE Antiretroviral agents remain the cornerstone of HIV treatment and prevention. All HIV-infected individuals with detectable plasma virus should receive treatment with recommended initial regimens consisting of an InSTI plus 2 NRTIs. Preexposure prophylaxis should be considered as part of an HIV prevention strategy for at-risk individuals. When used effectively, currently available ARVs can sustain HIV suppression and can prevent new HIV infection. With these treatment regimens, survival rates among HIV-infected adults who are retained in care can approach those of uninfected adults.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Huldrych F. Günthard, MD, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Rämistrasse 100, 8091 Zürich, Switzerland (huldrych.guenthard@usz.ch).

There have been substantial advances in the use of antiretroviral drugs (ARVs) for the treatment and prevention of HIV infection since the last version of these recommendations in 2014,[1] warranting an update to the recommendations.

With rare exception, all HIV-infected individuals with detectable viremia, regardless of their CD4 cell count, should begin antiretroviral therapy (ART) as soon as possible after diagnosis to prevent disease progression, improve clinical outcomes, and limit transmission. This recommendation is strongly supported by recent large randomized clinical trials.[2,3] New drugs that combine excellent potency with greater convenience, safety, and tolerability make lifelong viral suppression achievable and reduce the risk of viral resistance. In HIV-infected persons, ART is effective in preventing HIV transmission[1,4,5] and provides individual and public health benefits. Antiretroviral therapy for individuals at risk of acquiring HIV infection (as postexposure prophylaxis [PEP] or preexposure prophylaxis [PrEP]) prevents HIV acquisition.

This revision of the recommendations discusses the latest developments in uses of ARVs, summarizing current knowledge on the following: when to start therapy, including optimal initial treatment regimens; ART for patients with opportunistic infections (OIs); when and how to switch ART; laboratory monitoring; engagement in care and ART adherence; and prevention of HIV infection.

Methods

Recommendations were developed by an international panel of 14 volunteer experts in HIV research and patient care appointed by the International Antiviral Society–USA. Potential members were screened for expertise in the field, involvement in research and care, financial relationships with commercial companies, and ability to work toward consensus. The panel convened in person and by conference calls from late 2015 to mid-2016. Teams for each major section, each with a lead writer, evaluated relevant evidence and drafted recommendations for full panel review.

Evidence used was published in the scientific literature, presented at major scientific conferences, or released as safety reports by regulatory agencies or data and safety monitoring boards since 2014.[1] Literature searches in PubMed and EMBASE were designed by an expert in systematic reviews to capture publications relevant to ART in HIV infection since the 2014 iteration of the recommendations[1] through April 2016. New evidence was considered in conjunction with evidence used for prior reports.[1] Approximately 320 relevant citations were identified by 1 author (P.V.) from an initial list of more than 3200. Relevant abstracts publicly presented at scientific conferences since June 2014 were identified by panel members. Manufacturers of ARVs provided lists of relevant scientific publications or abstracts presented at peer-reviewed conferences.

These recommendations are focused on adults (defined as aged ≥18 years) with or at risk of HIV infection in settings in which most ARVs are available (approved by regulatory bodies or in expanded access) or in late-stage development (new drug application filed). Recommendations were made by consensus and rated according to the strength of the recommendation and the quality of the evidence (**Table 1**). Recommendations that have not changed substantially or for which few relevant data have become available since 2014 are included in the 2014 treatment recommendations[1] along with detailed discussion and citations. Where appropriate, prior citations were included. Further details about the recommendations development process, panel selection, summary of evidence collection and literature search strategies, and the sponsor (International Antiviral Society–USA) and its policies are available in the Supplement.

Table 1. Strength of Recommendation and Quality of Evidence Rating Scale[a]

Rating	Definition
Strength of recommendation	
A	Strong support for the recommendation
B	Moderate support for the recommendation
C	Limited support for the recommendation
Quality of evidence	
Ia	Evidence from ≥1 randomized clinical trials published in the peer-reviewed literature
Ib	Evidence from ≥1 randomized clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

[a] Adapted in part from the Canadian Task Force on Periodic Health Examination.[6]

When to Start

Initiation of Therapy

Recommendations for when to start ART are summarized in **Box 1**. ART is recommended for all HIV-infected patients with detectable viremia, regardless of CD4 cell count (evidence rating AIa). Randomized clinical trial data now further confirm previous recommendations for early initiation of ART in adults[1,7] because of the individual-level clinical benefit (reduction in AIDS-related events, non–AIDS-related events, and all-cause mortality) (**Table 2**)[2,3,8] and a decreased risk of HIV transmission.[4]

Patients should understand the goals of treatment and be willing to initiate therapy. Baseline resistance testing is recommended for all patients, but initiating therapy prior to availability of the results may be appropriate in some cases. Recent data suggest little transmitted drug resistance to integrase strand transfer inhibitors (InSTIs) and protease inhibitors (PIs) but not nonnucleoside reverse transcriptase inhibitors (NNRTIs).[9-11]

Current Investigational Approaches to Starting Therapy

Initiation of ART is recommended as soon as possible in the setting of acute HIV infection (evidence rating BIII).[1] Initiation prior to the development of HIV antibody positivity reduces the size of the latent HIV reservoir, reduces immune activation, and may protect against infection of central memory T cells. Benefits are maximal during the first few weeks after HIV infection but are apparent up

to the first 6 months after infection.[12-16] However, early therapy does not prevent the establishment of the latent HIV reservoir. Planned discontinuation of early ART after a specific duration of treatment is not recommended outside research settings; the benefits do not persist and the subsequent viral rebound is associated with increased clinical events and the potential for transmission (evidence rating AIa).[16-18]

Initiation of ART on the same day as diagnosis of HIV infection has been implemented in several cities.[19,20] Evaluation of the long-term effectiveness and limitations of this strategy is needed.

Initiation of ART in "elite controllers" (defined as patients with confirmed HIV infection and persistent undetectable HIV RNA without ART) remains controversial. Elite controllers may still benefit from ART because they have higher levels of immune activation and an increased risk of cardiovascular disease and hospitalization compared with individuals achieving virologic suppression with ART.[21] Initiation of treatment, however, is recommended for infected persons who have persistent undetectable viral load without ART but have declining CD4 cell counts (evidence rating BIII).

Box 1. Recommendations for When to Start Antiretroviral Therapy[a]

- Antiretroviral therapy (ART) is recommended for all viremic patients with established HIV infection, regardless of CD4 cell count (evidence rating AIa).
- Initiation of ART is recommended as soon as possible in the setting of acute HIV infection (evidence rating BIII).
- Planned discontinuation of early ART after a specific duration of treatment is not recommended outside a research setting (evidence rating AIa).[b]
- Initiation of ART is recommended for individuals who have persistent undetectable viral load without ART but have declining CD4 cell counts (evidence rating BIII).

[a] See text for essential details and cautions.

[b] The recommendation or the evidence rating has not changed substantially since the 2014 report.

Recommended Initial Regimens

Recommendations for initial antiretroviral regimens are summarized in **Box 2**. Among adherent individuals, initial ART with 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a third active drug from a different class achieves and maintains similar virologic suppression rates in nearly all patients.[22-26] Clinicians and patients have many options and may select a regimen based on considerations other than antiviral potency. Considerations include short- and long-term adverse effects, ease of administration, drug interactions, risk of resistance if virologic failure occurs, and cost. Patients with more than 100 000 HIV RNA copies/mL or fewer than 200 CD4 cells/μL remain a subset in whom ART potency is particularly important, as certain regimens have suboptimal virologic suppression in this setting.[1,7,27-35]

Optimal Initial Regimens

InSTI-based regimens are optimal for initial therapy. Recommended initial ART for most patients are (regimens are listed in alphabetic order by InSTI component; see **Table 3**) dolutegravir/abacavir/lamivudine (evidence rating AIa), dolutegravir plus tenofovir alafenamide (TAF)/emtricitabine (AIa), elvitegravir/cobicistat/TAF/emtricitabine (evidence rating AIa), and raltegravir plus TAF/emtricitabine (evidence rating AIII). (Components separated with a slash [/] indicate that they are available as coformulations.)

If TAF is not available, tenofovir disoproxil fumarate (TDF) is an effective and generally well-tolerated option. Given the limited long-term experience with TAF, some clinicians may prefer to continue using TDF pending broader experience with TAF in clinical practice.

InSTIs as Components of the Initial Regimen

In the SINGLE study, dolutegravir plus abacavir/lamivudine was superior to efavirenz/TDF/emtricitabine.[36] Similar results were observed in the FLAMINGO study (comparing dolutegravir with ritonavir-boosted [/r] darunavir),[37] in the WAVES study (comparing cobicistat-boosted [/c] elvitegravir with atazanavir/r in HIV-infected women),[38] and in the AIDS Clinical Trials Group 5257 study (comparing raltegravir with atazanavir/r or darunavir/r).[39]

No clinical trial has directly compared all 3 currently available InSTIs. In treatment-naive patients, dolutegravir was noninferior to raltegravir, with no resistance to dolutegravir observed in that treatment group.[40] In treatment-experienced patients, dolutegravir was superior to raltegravir[41] and elvitegravir was noninferior to raltegravir.[42] The InSTIs differ in several important features that may influence treatment choice (**Table 4**).

Abacavir as a Component of the Initial Regimen

Abacavir is a component of the recommended regimen of dolutegravir/abacavir/lamivudine. Approximately half of individuals who are positive for the HLA-B*5701 allele experience a hypersensitivity reaction to abacavir that may be life threatening.[44] HLA-B*5701 testing should be performed prior to abacavir use (evidence rating AIa); those who test positive should not be given abacavir (evidence rating AIa). Allergy to abacavir should be listed in the medical record.

Although some prior comparisons of abacavir/lamivudine and TDF/emtricitabine demonstrated an efficacy advantage of TDF/emtricitabine,[45,46] these differences have not been observed in studies that use dolutegravir. In the SINGLE study, all patients in the dolutegravir-containing group used abacavir/lamivudine.[36] In the SPRING-2 and FLAMINGO studies, a minority of dolutegravir-treated patients used abacavir/lamivudine, and no differences in efficacy were found based on NRTI selection.

The association between abacavir and an increased risk of myocardial infarction remains controversial.[1,7,34,35] More studies have now been published describing the association,[47-49] but the data remain inconclusive. For now, abacavir should be used with caution in patients who have or who are at high risk of cardiovascular disease.

TAF as a Component of the Initial Regimen

Compared with TDF, TAF yields a lower plasma level of tenofovir and higher intracellular concentration of the active antiviral component tenofovir diphosphate. This results in fewer tenofovir-

Table 2. Summary Results of 3 Key Randomized Clinical Trials of Immediate vs Deferred Antiretroviral Therapy (ART) in ART-Naive HIV-Infected Individuals

Source	No. of Participants in Study (CD4 Cell Count Parameter)	Duration of Follow-up, mo	Study End Point	No. (%) With Outcome in Immediate ART Group	No. (%) With Outcome in Deferred ART Group	Hazard Ratio (95% CI) for Immediate vs Deferred ART
Lundgren et al,[2] 2015	4685 (>500/μL)	36	Primary end point (AIDS, serious non-AIDS-related events, death)	42 (1.8) [0.6/100 patient-years of observation]	96 (4.1) [1.38/100 patient-years of observation]	0.43 (0.3-0.62)
			AIDS-related events	14 (0.6)	50 (2.1)	0.28 (0.15-0.50)
			Serious non-AIDS-related events	29 (1.3)	47 (2.0)	0.61 (0.38-0.97)
			All-cause mortality	12 (0.5)	21 (0.9)	0.58 (0.28-1.17)
Danel et al,[3] 2015	2056	30	Primary end point (AIDS, non-AIDS-related cancer or bacterial disease, death)	64 (6.2) [2.8/100 patient-years of observation]	111 (10.9) [4.9/100 patient-years of observation]	0.56 (0.41-0.76)
			AIDS-related events	33 (3.2)	65 (6.4)	
			Mortality	21 (2.0)	26 (2.5)	
	843 (Baseline >500/μL)	30	Subgroup of participants with baseline CD4 cell count >500/μL (primary end point)	23 (2.2) [2.4/100 patient-years of observation]	38 (3.7) [4.1/100 patient-years of observation]	0.56 (0.33-0.94)
Grinsztejn et al,[8] 2014	1763 (350/μL-550/μL)	24	Primary end point (AIDS, non-AIDS-related events, severe bacterial infections, death)	57 (6.4)	77 (8.8)	0.73 (0.52-1.03)
			AIDS	40 (4.5)	61 (7.0)	0.64 (0.43-0.96)
			Non-AIDS-related events	12 (1.4)	9 (1.0)	1.35 (0.57-3.19)
			Death	11 (1.2)	15 (1.7)	0.73 (0.34-1.59)

associated toxic effects, such as proximal renal tubular toxicity and reductions in bone mineral density. One report suggested the possibility of elevated liver enzymes with TDF use, but the clinical significance is uncertain.[50]

TAF and TDF were compared in prospective clinical trials of initial therapy[51,52] and in switch strategies from TDF in patients with virologic suppression and no history of resistance or treatment failure.[53,54] To date, only elvitegravir/c has been used in studies of TAF as initial therapy, but a broader range of third drugs has been used in switch studies.

Compared with TDF, TAF has little or no effect on bone density and little or no kidney toxicity. Specifically, proximal tubulopathy has not been observed to date with TAF, which has less effect on renal tubular and overall proteinuria and estimated glomerular filtration rate (eGFR) than TDF. TAF reduces lipids less than TDF; however, this difference does not affect the ratio of total to high-density lipoprotein cholesterol. To date, no cases of clinical renal disease are directly ascribed to TAF. Tolerability of TAF and TDF is comparable, as are rates of HIV suppression, resistance with virologic failure, and increases in CD4 cell count.

The daily dose of TAF (25 mg or 10 mg) is lower than that of TDF (300 mg). For HIV treatment, TAF is currently available only in coformulations, consisting of emtricitabine/TAF; rilpivirine/emtricitabine/TAF; and elvitegravir/cobicistat/emtricitabine/TAF. Unlike TDF, TAF should not be used with rifamycins, and there are limited data on its safety and efficacy for pregnant women.

Non–InSTI-Containing (or Non–NRTI-Containing) Initial Regimens

Several non–InSTI-containing regimens suppress HIV RNA in the majority of patients who are adherent to therapy. These may be optimal for a given patient based on individual clinical characteristics, preferences, or owing to financial considerations or lack of InSTI availability. These regimens are acceptable therapeutic options. These options are listed in **Table 5**.

Initial therapy with 2 active drugs is under investigation. This strategy may offer cost or toxicity advantages over the current 3-drug regimens.[56] To date, only 2 adequately powered randomized clinical trials have demonstrated noninferior outcomes of 2-drug therapy compared with 3-drug regimens. Lopinavir/r plus lamivudine was noninferior to lopinavir/r plus 2 NRTIs in one study,[57] and darunavir/r plus raltegravir was noninferior to darunavir/r plus 2 NRTIs in another.[58] However, these 2-drug regimens have limitations. Lopinavir/r induces relatively high rates of gastrointestinal adverse effects and hyperlipidemia. Darunavir/r plus raltegravir was associated with higher rates of treatment failure in patients with a CD4 cell count below 200/μL or an HIV RNA level above 100 000 copies/mL. A small single-group trial of dolutegravir plus lamivudine in 20 patients demonstrated promising results.[59]

Initial 2-drug regimens are recommended only in the rare situations in which a patient cannot take abacavir, TAF, or TDF (evidence rating BIa); [darunavir/c or darunavir/r] plus [raltegravir

Box 2. Recommendations for Initial ART Regimens[a]

- Recommended initial regimens (listed in alphabetic order by InSTI component):
  - Dolutegravir/abacavir/lamivudine (evidence rating AIa)
  - Dolutegravir plus TAF/emtricitabine (evidence rating AIa)[b]
  - Elvitegravir/cobicistat/TAF/emtricitabine (evidence rating AIa)[b]
  - Raltegravir plus TAF/emtricitabine (evidence rating AIII)
- HLA-B*5701 testing should be performed prior to abacavir use (evidence rating AIa); those who test positive should not be given abacavir (evidence rating AIa).
- Tenofovir disoproxil fumarate is not recommended for individuals with or at risk of kidney or bone disease (osteopenia or osteoporosis) (evidence rating BIII).
- Recommended initial regimens for individuals in whom an InSTI is not an option (listed in alphabetic order by InSTI component):
- Darunavir (boosted) plus TAF (or TDF)/emtricitabine or abacavir/lamivudine (evidence rating AIa)[b]
  - Efavirenz/TDF/emtricitabine (evidence rating AIa)
  - Rilpivirine/TAF (or TDF)/emtricitabine (evidence rating AIa)[b]
- Initial 2-drug regimens are recommended only in rare situations in which a patient cannot take abacavir, TAF, or TDF (evidence rating BIa).
- HIV-infected pregnant women should initiate ART for their own health and to reduce the likelihood of HIV transmission to their infant (evidence rating AIa).[c]
- For HIV-infected patients with hepatitis B virus coinfection should initiate ART that contains TDF or TAF (evidence rating AIa), lamivudine or emtricitabine, and a third component (evidence rating AIa).
- Entecavir may be used to treat hepatitis B virus infection (evidence rating AIII). If HIV RNA is not suppressed, entecavir should be avoided because it can select for drug-resistant HIV (evidence rating AIII).
- HIV-infected patients with hepatitis C virus coinfection should start an ART regimen with drugs that do not have significant drug interactions with hepatitis C virus therapies (evidence rating AIIa).
- Tenofovir disoproxil fumarate is not recommended for patients with osteopenia or osteoporosis (evidence rating BIII).
- Monitoring for development of kidney disease with estimated glomerular filtration rate, urinalysis, and testing for glycosuria and albuminuria or proteinuria is recommended when ART is initiated or changed and every 6 months (along with HIV RNA) once HIV RNA is stable (evidence rating BIII).
- Tenofovir disoproxil fumarate should be avoided or dose adjusted in patients with a creatinine clearance rate below 60 mL/min (evidence rating AIa).
- Tenofovir alafenamide is not recommended in patients with a creatinine clearance rate below 30 mL/min (evidence rating AIa).
- Tenofovir disoproxil fumarate or TAF should be discontinued if a patient's renal function worsens, particularly if there is evidence of proximal tubular dysfunction (evidence rating AIIa).
- HIV-infected patients with end-stage renal disease should be evaluated for kidney transplantation with expectation of high rates of patient and graft survival (evidence rating AIIa).

Abbreviations: ART, antiretroviral therapy; InSTI, integrase strand transfer; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a] See text for essential details and cautions. Components separated with a slash (/) indicate that they are available as coformulations.

[b] TDF may be substituted for TAF if TAF is not available for the patient.

[c] The recommendation or the evidence rating has not changed substantially since the 2014 report.

or dolutegravir] or plus [lamivudine or emtricitabine] may be considered, but the former strategy may be less effective in those with CD4 cell counts below 200/μL or HIV RNA levels above 100 000 copies/mL. Of note, there are no adequately powered studies of initial therapy of other listed 2-drug regimens besides darunavir/r plus raltegravir or lopinavir/r plus lamivudine; efficacy is assumed from other clinical trials.[57,58]

Special Considerations

Pregnancy

HIV-infected pregnant women should initiate ART for their own health and to reduce the likelihood of HIV transmission to the infant (evidence rating AIa). Nucleoside reverse transcriptase inhibitor options include abacavir/lamivudine (if the patient is HLA-B*5701 negative), TDF/emtricitabine, or zidovudine/lamivudine. Zidovudine/lamivudine is the regimen with the longest clinical experience, but it has more toxic effects. Raltegravir is the recommended InSTI for use during pregnancy. Recommended boosted PIs include atazanavir/r (once daily) or darunavir/r (twice daily). The recommended NNRTI is efavirenz when initiated after the first 8 weeks of pregnancy. If an HIV-infected woman who is taking efavirenz becomes pregnant, the regimen may be continued; changing it risks loss of virologic control.

Hepatitis B Virus Coinfection

HIV-infected patients with hepatitis B virus (HBV) coinfection should initiate a recommended ART regimen that contains TDF or TAF (evidence rating AIa), lamivudine or emtricitabine, and a third component.[60-62] Lamivudine and emtricitabine each have substantial antiviral activity against HBV. However, there is a high risk of HBV resistance and viral breakthrough if these drugs are used without TDF or TAF, and neither is recommended alone for HBV in coinfection. Entecavir may be used to treat HBV infection (evidence rating AIII). If HIV RNA is not suppressed, entecavir should be avoided because it can select for lamivudine- and emtricitabine-resistant HIV (evidence rating AIII).

Hepatitis C Virus Coinfection

HIV-infected patients with hepatitis C virus (HCV) coinfection should start an ART regimen with drugs that do not have significant drug interactions with HCV therapies (evidence rating AIIa). The recommended regimens that have the fewest drug interactions with current HCV treatments are dolutegravir/abacavir/lamivudine and dolutegravir or raltegravir plus TAF/emtricitabine. Clinicians should consult current HCV treatment guidelines prior to using any other ART regimens, particularly those that include NNRTIs, boosted HIV PIs, or elvitegravir/c.[63]

Bone Disease

Osteoporosis and fractures are increased with HIV infection.[64] During the first 1 to 2 years after initiation of ART, patients may lose 2% to 6% of their bone mineral density at the hip and spine. Patients who receive TDF-containing regimens have a greater initial decline in bone mineral density than those who take a TAF- or abacavir-containing regimen. For this reason, TDF is not recommended for patients with osteopenia or osteoporosis (evidence rating BIII).

Table 3. Recommended Initial Antiretroviral Therapy Regimens[a]

Regimen	Rating
Dolutegravir/abacavir/lamivudine	AIa
Dolutegravir plus tenofovir alafenamide/emtricitabine[b]	AIa
Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine[b]	AIa
Raltegravir plus tenofovir alafenamide/emtricitabine[b]	AIII

[a] Regimens are listed in alphabetic order by integrase strand transfer inhibitor component. Components separated with a slash (/) indicate that they are available as coformulations.

[b] In settings in which tenofovir alafenamide/emtricitabine is not available, tenofovir disoproxil fumarate (with emtricitabine or lamivudine) remains an effective and generally well-tolerated option. Given the limited long-term experience with tenofovir alafenamide, some clinicians may prefer to continue using tenofovir disoproxil fumarate pending broader experience with tenofovir alafenamide in clinical practice.

Kidney Disease

Monitoring for development of kidney disease with eGFR, urinalysis, and testing for glycosuria and albuminuria or proteinuria is recommended when ART is initiated or changed and every 6 months (along with HIV RNA) once HIV RNA is stable (evidence rating BIII).[65] In cohort studies, TDF (especially with a boosted PI) increased the risk of chronic kidney disease.[66] Tenofovir disoproxil fumarate is not recommended for patients with an eGFR below 60 mL/min.[65] The options are abacavir (which does not require dose adjustment in this setting) or TAF (if creatinine clearance is above 30 mL/min) (evidence rating AIIa). Long-term data on TAF in patients with preexisting renal disease are limited.[67] Tenofovir disoproxil fumarate or TAF should be discontinued if renal function worsens, particularly if there is evidence of proximal tubular dysfunction (eg, euglycemic glycosuria or urinary

Table 4. Advantages and Disadvantages of Currently Available Integrase Strand Transfer Inhibitors

	Dolutegravir	Elvitegravir	Raltegravir
Year of US Food and Drug Administration approval	2013	2012	2007
Advantages	Superior to efavirenz and ritonavir-boosted darunavir in comparative clinical trials[36,37] Once-daily dosing Coformulated with abacavir/lamivudine as part of a complete initial regimen Dolutegravir (not coformulated) pill size is small Lowest risk of resistance with virologic failure[36,37,40,43] Relatively few drug interactions Can be taken with or without food Superior to raltegravir in treatment-experienced patients	Superior to ritonavir-boosted atazanavir in comparative clinical trial in HIV-infected women[38] Once-daily dosing Coformulated with tenofovir disoproxil fumarate/emtricitabine or tenofovir alafenamide/emtricitabine as a complete regimen	Superior to ritonavir-boosted atazanavir and ritonavir-boosted darunavir in comparative clinical trial[39] Longest safety record Fewest drug interactions Can be taken with or without food
Disadvantages	Only available coformulation is with abacavir/lamivudine Raises serum creatinine owing to inhibition of tubular secretion of creatinine Higher rates of insomnia and headache than comparators in some studies[36,37] Largest tablet among coformulated single-pill regimens	Requires pharmacokinetic boosting with cobicistat or ritonavir for once-daily dosing Most drug interactions Cobicistat raises serum creatinine owing to inhibition of tubular secretion of creatinine Should be taken with food	Currently must be taken twice daily (formulation consisting of 2 pills given once daily in development) Not coformulated as part of a complete regimen

Table 5. Advantages and Disadvantages of Initial Antiretroviral Therapy Options for Patients in Whom InSTIs Are Not an Option[a]

	Darunavir (Boosted With Cobicistat or Ritonavir) Plus TAF/Emtricitabine, TDF/Emtricitabine, or Abacavir/Lamivudine[b]	Efavirenz/TDF/Emtricitabine	Rilpivirine/TAF (or TDF)/Emtricitabine
Advantages	Low risk of resistance with virologic failure, even with intermittent adherence	High efficacy in patients with baseline HIV RNA >100 000 copies/mL Extensive experience in patients with concomitant tuberculosis Widely available globally	Lowest risk of rash among NNRTI-based therapies Low risk of metabolic adverse effects Smallest tablet among single-pill regimens
Disadvantages	Requires pharmacokinetic boosting; many drug interactions Ritonavir-boosted darunavir inferior to raltegravir and dolutegravir in separate comparative clinical trials[37,39] Results of comparative, fully powered studies of cobicistat-boosted darunavir as initial therapy are not yet available	Relatively high rate of rash No single-tablet form available with TAF High rates of neuropsychiatric adverse effects Increased risk of suicidality in 1 study[55]; avoid in patients with history of depression	Not recommended for patients with HIV RNA >100 000 copies/mL or CD4 cell count <200/μL owing to increased risk of virologic failure Must be taken with a meal to optimize absorption Should not be administered with proton pump inhibitors; stagger dosing if given with an H_2 blocker

Abbreviations: InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a] Nonnucleoside reverse transcriptase inhibitor–based regimens should not be used without baseline resistance data because of the possible presence of transmitted NNRTI-resistant virus. In the rare circumstance in which maraviroc might be included in initial therapy, initiation should not occur before confirmation of CC chemokine receptor 5 tropism.

[b] Cautions on the use of abacavir and TAF or TDF are described in the text.

phosphate wasting) (evidence rating AIIa). The safety of TAF in patients with active TDF-associated proximal tubulopathy has not been determined. If possible, TAF should be initiated only after tubulopathy has resolved, with monitoring for recurrence. HIV-infected patients with end-stage renal disease should be evaluated for kidney transplantation with the expectation of high rates of patient and graft survival (evidence rating AIIa).

Cost Considerations

In highly resourced countries, approximately 75% to 80% of annual HIV care expenditures are spent on medications.[68] Even at full price, ART is cost-effective.[69] In the United States, drug pricing discounts are common, but the amount of discount remains unknown to clinicians and patients, making it difficult to use pricing as a component of treatment decisions.

As more drugs become available in less-expensive generic formulations, payers may begin to use "societal benefit" as a criterion for selection of the initial regimen. One modeling study showed a savings of up to $900 million annually with routine use of a generic efavirenz-based regimen in the United States over a branded version of the same regimen.[70] Although relative efficacy in viral suppression is lower with an efavirenz-based regimen than with InSTI-based regimens, the differences are modest and driven by tolerability rather than potency.[71]

Where resource constraints limit the ability of a health system to provide widespread treatment to all HIV-infected persons, a strategy of using generic formulations of recommended regimens first with use of more expensive drugs for those who demonstrate intolerance may be reasonable. Such policy decisions should be determined in consultation with HIV experts in the locale where the policy is being considered.

Interface of ART and OIs

When to Start ART in the Setting of Active OIs

Recommendations for ART in the setting of OIs are summarized in Box 3. ART should be started as soon as possible but within the first 2 weeks after diagnosis for most OIs,[1] with the possible exception of acute cryptococcal meningitis (evidence rating AIa). In a randomized clinical trial of ART initiation in the setting of cryptococcal meningitis in resource-constrained settings, mortality was higher when ART was started within the first 1 to 2 weeks of diagnosis; mortality was lower when ART was delayed until 5 weeks after diagnosis.[72] However, in the United States, Canada, and Europe, where there may be greater access to optimal antifungal therapy (eg, flucytosine),[73] frequent monitoring, and appropriate management of high intracranial pressure and other underlying conditions, earlier initiation of ART, within 2 weeks of diagnosis, is preferred.[74] Although a randomized clinical trial found no survival benefit of early initiation of ART for HIV-infected persons with active tuberculosis and CD4 cell counts greater than 220/μL,[75] there was no increased harm, and the improved survival observed in the SAPiT, CAMELIA, and STRIDE trials, particularly for those with lower CD4 cell counts,[1,76-78] supports the recommendation to start ART within the first 2 weeks of initiation of tuberculosis treatment for those with CD4 cell counts of 50/μL or less and within the first 2 to 8 weeks for those with CD4 cell counts above 50/μL (evidence rating AIa). Of note, earlier initiation of ART in persons with active tuberculosis, particularly tuberculosis meningitis, may be associated with higher rates of immune reconstitution inflammatory syndrome and may complicate management of adverse drug reactions,[79] thus mandating careful monitoring in this setting.

Box 3. ART and Opportunistic Infection Recommendations[a]

- ART should be started within the first 2 weeks after diagnosis for most acute opportunistic infections, with the possible exception of acute cryptococcal meningitis (evidence rating AIa).[b]
- ART should be started within the first 2 weeks of initiation of tuberculosis treatment for those with CD4 cell counts of 50/μL or less and within the first 2 to 8 weeks for those with CD4 cell counts above 50/μL (evidence rating AIa).
- Neither tenofovir alafenamide nor cobicistat-boosted elvitegravir is recommended with rifamycin drugs (evidence rating AIIb). A boosted protease inhibitor–based regimen should be used only if an integrase strand transfer inhibitor is not an option, and rifabutin, 150 mg/d, should be substituted for rifampin in the antituberculosis regimen (evidence rating AIa).
- Primary *Mycobacterium avium* complex prophylaxis is not recommended if effective ART is initiated immediately and viral suppression achieved (evidence rating AIIa).
- Primary *Pneumocystis* pneumonia prophylaxis is recommended for patients who meet CD4 cell count criteria (evidence rating AIa), even if taking ART.

Abbreviation: ART, antiretroviral therapy.

[a] See text for essential details and cautions.

[b] The recommendation or the evidence rating has not changed substantially since the 2014 report.

Recommended Initial ART in the Setting of OIs

Drug interactions and tolerability are important considerations when choosing an initial ART regimen in persons with an acute OI. Azole antifungal agents and rifamycins are of particular concern. The choices for ART in the setting of rifamycin-based antituberculosis therapy have been expanded; efavirenz, 600 mg daily; raltegravir, 400 mg twice daily; or dolutegravir, 50 mg twice daily in combination with 2 NRTIs are acceptable, with InSTI-based regimens recommended.[76-78,80-83] Neither TAF nor elvitegravir/c is recommended with rifamycin drugs because of potential adverse drug interactions (evidence rating AIIb). A boosted PI–based regimen should be used only if an InSTI-based regimen is not an option, and rifabutin, 150 mg daily, should be substituted for rifampin in the antituberculosis regimen (evidence rating AIa).[84-86]

A 3-month, once-weekly regimen of isoniazid and rifapentine for treatment of latent tuberculosis infection is as effective as 9 months of isoniazid alone in HIV-infected individuals.[87-89] High-dose daily rifapentine can be safely administered with efavirenz, allowing the 3-month regimen to be administered with efavirenz-based ART.[80,90] Although raltegravir exposure was increased when administered with once-weekly rifapentine,[91] the regimen was well tolerated, supporting use of raltegravir-based regimens. There are no pharmacokinetic data on rifapentine with dolutegravir. However, extrapolation from available data on rifampin and the similarities between rifapentine and rifampin pharmacokinetics supports dolutegravir use in this context, with similar dose adjustments as suggested for antituberculosis therapy.

Box 4. Recommendations for When and How to Switch Antiretroviral Regimens[a]

- Data support possible switching from an older regimen to a single-pill regimen in certain patients with virologic suppression (see text).[b]
- Induction maintenance strategies (switching from 3- to 2-drug regimens in patients with virologic suppression [see text]) are not recommended at this time (evidence rating BIIa).
- Patients taking efavirenz should be questioned carefully about the possibility of subtle neuropsychiatric adverse effects (eg, dizziness, sleep disturbances, cognitive changes, depression) that they may be unaware of or may not attribute to the drug (evidence rating BIII).
- Review of treatment history and results of prior resistance tests is recommended before any treatment switches are made (evidence rating AIa).
- If there is no increase in price, switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide is reasonable even if patients are not experiencing TDF-related toxic effects (evidence rating BIa).
- Switching from a boosted protease inhibitor to a nonnucleoside reverse transcriptase inhibitor or an integrase strand transfer inhibitor (with the possible exception of dolutegravir) or switching from twice-daily ritonavir-boosted darunavir to once-daily cobicistat-boosted darunavir is not recommended without consideration of a patient's viral resistance profile (evidence rating AIII).

[a] See text for essential details and cautions.

[b] The recommendation or the evidence rating has not changed substantially since the 2014 report.

CD4 Cell Count Monitoring and Primary OI Prophylaxis

Recommendations regarding when to initiate, whether to continue, and when to stop prophylaxis for OIs have been based on CD4 cell counts prior to and after initiation of ART. With ART recommended for all HIV-infected persons regardless of CD4 cell count, the incidence of AIDS-associated OIs and associated mortality continues to decline. For persons achieving virologic suppression with ART, the incidence of *Mycobacterium avium* complex (MAC) disease has declined sufficiently that mortality is not substantially different once MAC disease develops for those who did vs did not receive primary MAC prophylaxis.[92,93] Thus, primary MAC prophylaxis is not recommended if effective ART is initiated immediately (evidence rating AIIa). Although similar trends are seen with *Pneumocystis jirovecii* pneumonia as with MAC,[92,94] *Pneumocystis* pneumonia is the most common AIDS-related OI and carries a higher risk of early mortality than MAC disease.[92] In the absence of stronger data, initiating primary prophylaxis for *Pneumocystis* pneumonia is still recommended for those who meet CD4 cell count criteria (evidence rating AIa).

When and How to Switch

Recommendations for when and how to switch antiretroviral regimens are summarized in **Box 4**. With improvements in ART, the need to switch therapy because of virologic failure and drug resistance has decreased. However, these improvements provide a rationale for switching therapy in some patients who have virologic suppression with older regimens that are less convenient or that have more adverse or toxic effects. Reasons to consider switching therapy in such patients include adverse effects, simplification (reducing doses or pills), drug-drug interactions, pregnancy or plans for pregnancy, and food restrictions.

Study data support switching from an older regimen to one of a number of single-pill regimens: dolutegravir/abacavir/lamivudine,[95] elvitegravir/cobicistat/emtricitabine/TAF,[53] elvitegravir/cobicistat/emtricitabine/TDF,[96,97] or rilpivirine/emtricitabine/TDF.[98] Data also support a switch from suppressive TDF/emtricitabine-based regimens to TAF/emtricitabine-based regimens.[60] The lack of randomized clinical trial data does not preclude the possibility of a switch, provided certain caveats are considered.

Induction maintenance approaches have been evaluated in which patients with virologic suppression switch from a 3-drug to a 2-drug maintenance regimen.[99-102] Although trials provide some support for this approach, it remains investigational, and induction maintenance strategies are not recommended at this time (evidence rating BIIa).

For patients experiencing adverse effects or drug toxicities or requesting modification or simplification of their regimen, the decision to switch is relatively easy. Situations exist in which practitioners should recommend a switch even for patients who are satisfied with their current regimen and appear to be doing well. These include when patients are taking regimens containing stavudine, didanosine, or zidovudine, largely because of long-term toxic effects, or older PIs that have higher pill burdens and greater metabolic toxicities than darunavir or atazanavir. Some drugs that are no longer recommended for initial use may often be safely continued for patients who are tolerating them. For example, although nevirapine and efavirenz have substantial early toxic effects, they are safe and tolerable in the long term. Patients taking efavirenz should be questioned carefully about the possibility of subtle neuropsychiatric adverse effects (eg, dizziness, sleep disturbances, cognitive changes, depression) that they may be unaware of or may not attribute to the drug (evidence rating BIII).

With the availability of TAF in its coformulations, it is possible to switch from TDF to TAF. Although the presumption of greater renal and bone safety is primarily based on surrogate markers (ie, bone density as a marker for fracture risk; eGFR and proteinuria for renal safety), these markers consistently suggest superior safety of TAF vs TDF. One exception may be modest lipid elevations due to the loss of the lipid-lowering effects of TDF. If there is no increase in the price of TAF vs that of TDF, switching from TDF to TAF is reasonable even if patients are not experiencing TDF-related toxic effects (evidence rating BIa).

For patients with virologic suppression, it is important to consider the possibility of drug resistance and whether the genetic barriers to resistance of the existing and proposed switch regimens are high or low. The risk of switching from a high-barrier regimen to a low-barrier regimen in patients with preexisting drug resistance has been well demonstrated.[103] When possible, switches to a regimen with a lower resistance barrier should be made only after reviewing the treatment and resistance history (evidence rating AIa). When this information is not available, a proviral DNA genotype test may be helpful. The clinical utility of these assays has not yet been established, but they may be useful in detecting mutations that have been archived in resting CD4 cells but that are no longer detectable by standard commercial resistance assays.[104,105] Results must be in-

terpreted with caution because they can sometimes fail to detect existing mutations.[106] Some switches in the setting of viral suppression may be safe regardless of resistance (eg, TDF to TAF, efavirenz to rilpivirine or etravirine, raltegravir or elvitegravir to dolutegravir, or lopinavir/r to boosted darunavir). Switching from a boosted PI to an NNRTI or an InSTI (with the possible exception of dolutegravir) or switching from twice-daily darunavir/r to once-daily darunavir/c is not advised without considering resistance history because of the reduced resistance barrier of the regimen (evidence rating AIII).

The drug-drug interactions that affect the choice of initial regimen also must be considered when switching. Whether baseline viral load should be considered before switching therapy is not clear; baseline HIV RNA levels above 100 000 copies/mL were not associated with virologic failure when patients with virologic suppression with a PI-based regimen switched to a rilpivirine-containing regimen.[98]

The approach to virologic failure of an initial NNRTI-, PI-, or InSTI-based regimen has been addressed previously.[1] Failure of initial regimens that were chosen based on baseline resistance test results is generally due to poor adherence or, less commonly, to drug-drug interactions. Thus, adherence and drug interactions must be addressed before initiating the new regimen.

Laboratory Monitoring

Initiation of Therapy

Recommendations for laboratory monitoring are summarized in Box 5. As close to the time of HIV diagnosis as possible and prior to beginning ART, CD4 cell count, plasma HIV RNA, serologies for hepatitis A, B, and C, serum chemistries, estimated creatinine clearance, complete blood cell count, and urine glucose and protein should be measured (evidence rating AIII). Genotypic resistance assays for reverse transcriptase and protease should be ordered for all patients (evidence rating AIIa). Transmitted resistance to InSTIs has been documented but is uncommon at present, with little increase over time[107-109]; thus, routine pretreatment screening for integrase resistance is not currently recommended unless there is reason to believe that the infecting virus may have come from a source in whom InSTI-containing treatment failed (evidence rating BIII).[1] Screening for syphilis and 3-site (as appropriate) mucosal nucleic acid amplification testing for chlamydia and gonorrhea should also occur at the time of HIV diagnosis, and a fasting lipid profile should be obtained (evidence rating AIII). Other laboratory assessments should be individualized, in keeping with current guidelines.[110,111] HLA-B*5701 and CC chemokine receptor 5 tropism testing results must be confirmed prior to initiating therapy with abacavir and maraviroc, respectively.[1]

If ART is being initiated on the first clinic visit, all laboratory specimens should be drawn prior to the first dose of ART; resistance testing results should be used to modify the regimen as necessary (evidence rating AIII). A similar process should be used for rapid ART initiation for acute or advanced HIV infection.

Box 5. Recommendations for Laboratory Monitoring[a]

- Recommended pre-ART tests include CD4 cell count, plasma HIV-1 RNA, serologies for hepatitis A, B, and C, serum chemistries, estimated creatinine clearance rate, complete blood cell count, urine glucose and protein, sexually transmitted infection screening, and fasting lipid profile (evidence rating AIII).
- Genotypic testing for reverse transcriptase and protease resistance mutations is recommended prior to treatment initiation (evidence rating AIIa).
- Routine screening for integrase resistance is currently not recommended prior to treatment initiation unless the source virus is suspected to have been from someone in whom treatment containing an integrase strand transfer inhibitor failed (evidence rating BIII).
- Screening for syphilis and 3-site (as appropriate) mucosal nucleic acid amplification testing for chlamydia and gonorrhea should occur at the time of HIV diagnosis and a fasting lipid profile should be obtained (evidence rating AIII).
- If ART is initiated on the first clinic visit, all laboratory specimens should be drawn prior to the first dose of ART; resistance testing results should be used to modify the regimen as necessary (evidence rating AIII).
- HIV RNA level should be monitored every 4 to 6 weeks after treatment is initiated or changed until virus is undetectable (evidence rating AIa).[b]
- Therapeutic drug monitoring is not recommended except in specific circumstances (evidence rating BIII).[b]
- After viral suppression is achieved, HIV RNA should be monitored every 3 months until suppressed for 1 year and at least every 6 months thereafter for adherent patients who remain clinically stable (evidence rating AIII).
- If pretreatment CD4 cell count is below 200/μL, reassessment is recommended every 3 to 4 months until viral load is reliably suppressed and CD4 cell count is above 350/μL for 1 year. Thereafter, CD4 cell counts should be assessed at 6-month intervals until virus has been suppressed for at least 2 years and CD4 cell count is persistently stable above 500/μL (evidence rating AIII).
- When virus has been suppressed for at least 2 years and CD4 cell count is persistently above 500/μL, repeat monitoring of CD4 cell count is not recommended unless virologic failure (evidence rating AIIa) or intercurrent immunosuppressive conditions occur or immunosuppressive treatments are initiated (evidence rating AIII).
- If the HIV RNA level remains above the limit of quantification by 24 weeks after starting new treatment or if rebound above 50 copies/mL occurs at any time, the assay should be repeated within 4 weeks to exclude impending virologic failure (evidence rating AIIa).
- Tropism testing is recommended at the time of virologic failure of a CC chemokine receptor 5 inhibitor (evidence rating AIa).
- For patients with persistent quantifiable HIV RNA between 50 and 200 copies/mL, reassessment for causes of virologic failure, evaluation again within 4 weeks, and close monitoring are recommended (evidence rating BIII).[b]

Abbreviation: ART, antiretroviral therapy.

[a] See text for essential details and cautions.

[b] The recommendation or the evidence rating has not changed substantially since the 2014 report.

Ongoing Therapy

HIV RNA level should be monitored every 4 to 6 weeks after treatment is initiated or changed until it is undetectable, generally below 20 to 50 copies/mL (evidence rating AIa). Virologic suppression should occur within 24 weeks of ART initiation even when initiated during acute infection.[112] Failure to achieve suppression by 24 weeks should prompt evaluation for virologic failure. After suppression is achieved, HIV RNA should be monitored every 3 months

until suppression has been sustained for 1 year and at least every 6 months thereafter for adherent patients who remain clinically stable (evidence rating AIII). Therapeutic drug monitoring is not recommended except in specific circumstances, as previously described (evidence rating BIII).[1]

CD4 cell count is used to determine the need for OI prophylaxis. If pretreatment CD4 cell count is below 200/μL, reassessment is recommended every 3 to 4 months until HIV RNA is reliably suppressed and CD4 cell count is above 350/μL for 1 year. Thereafter, CD4 cell counts should be assessed at 6-month intervals until virus has been suppressed for at least 2 years and CD4 cell count is persistently stable above 500/μL (evidence rating AIII). Subsequently, repeat monitoring is not recommended unless virologic failure or intercurrent immunosuppressive conditions occur or immunosuppressive treatments are initiated (evidence rating AIII).[1,113] Monitoring for safety, including measures of renal and hepatic function and fasting lipids, should be individualized based on age, comorbid conditions, and concurrent medications. Screening for sexually transmitted infections should be conducted according to guidelines, local prevalence, and patient risk.[114]

Virologic Failure

Virologic failure is defined as a confirmed plasma HIV RNA above 200 copies/mL. If the HIV RNA level remains above the limit of quantification by 24 weeks or if rebound above 50 copies/mL occurs at any time, the assay should be repeated within 4 weeks to exclude impending virologic failure (evidence rating AIIa). The clinician should discuss adherence and tolerability with the patient and review the complete medication list, including nonprescribed supplements, to ensure that drug-drug interactions are not compromising therapeutic efficacy. Drug-food interactions should also be explored. Genotypic resistance testing should occur at the time of confirmed virologic failure, although amplification may not be successful for HIV RNA levels below 500 to 1000 copies/mL; proviral DNA assays to estimate archived resistance may be considered. With CC chemokine receptor 5 inhibitors, tropism testing is recommended at the time of virologic failure (evidence rating AIa). CD4 cell count assessment is recommended in the setting of viral rebound (evidence rating AIIa).

Management of Low-Level Viremia

Although any detectable virus has been associated with viral rebound in some studies,[115,116] measurable HIV RNA between 20 and 50 copies/mL did not increase the risk of virologic failure in 1 study.[117] Data are inconsistent about long-term effects of persistent HIV RNA between 50 and 200 copies/mL,[116,118] and current data are insufficient to guide clinical management. Such patients should be reassessed for causes of virologic failure, evaluated again within 4 weeks, and monitored closely (evidence rating BIII). Decisions to change therapy should be individualized based on ART options, resistance history, and clinical circumstances. Treatment should be changed in patients with persistent HIV RNA above 200 copies/mL.[119]

Viral Resistance

Although transmitted viruses with resistance mutations can revert to wild type, baseline resistance testing should be performed regardless of the duration of infection because many mutations have little effect on viral fitness and may persist for years.[120-122] Nonnucleoside reverse transcriptase inhibitor mutations are the most common transmitted resistance mutations (4.5%-10%); NRTI (4.0%-4.5%) and PI mutations are less common (2.8%-3.4%).[107,123] Virologic failure with an InSTI-containing regimen requires integrase resistance testing, as integrase resistance has been described in up to 6.8% of patients.[124] Resistance testing is less reliable if a patient has stopped ART for longer than 1 month when the sample is collected. The absence of resistance mutations does not confirm absence of resistance in this setting.

Engagement in Care and ART Adherence

Recommendations for engagement in care and ART adherence are summarized in **Box 6**.

Achieving the full benefits of treatment and prevention afforded by ART requires early diagnosis, rapid linkage to care, continuous retention in care, and uninterrupted access and adherence to ART. Late diagnosis and presentation for HIV care are global challenges that have improved only modestly over decades.[125,126] To avoid missed opportunities for earlier diagnosis,[127] routine opt-out HIV screening is recommended in primary medical care settings and emergency departments and for all pregnant women (evidence rating AIII).[128,129]

Even in highly resourced settings such as the United States, roughly 90% of new HIV infections are attributable to individuals with undiagnosed infection (30%) or who have received a diagnosis but are not engaged in HIV care (61%).[130] Systematic monitoring of time from diagnosis to care linkage, retention in care, ART adherence, and rates of viral suppression is recommended to identify and address barriers and to optimize individual and public health outcomes (evidence rating AIIa).[7]

Monitoring through integration of surveillance data with clinical data systems shows promise in improving health outcomes. Real-time surveillance-based messaging through an HIV health information exchange has increased engagement rates for individuals who were no longer in HIV care but were receiving non-HIV medical care at nearby sites.[131] Coordination with public health surveillance data systems is important, when possible, to improve linkage to, retention in, and reengagement in care.[7,132]

Evidence-based interventions to improve engagement in care are limited and have been described elsewhere.[133-135] Brief case management improved rates of linkage to care (within 6 months) and is recommended after diagnosis (evidence rating AIa).[136,137] Linkage to and retention in care may be enhanced through expedited care entry and rapid ART initiation within days of diagnosis,[19,20] and adequately powered intervention trials using this approach are planned. Patient navigation and intensive outreach can improve retention in care[138,139] but are most appropriate for a subset of patients at greatest risk because of the high resource requirements and cost. A patient navigation intervention with or without financial incentives improved engagement in care following inpatient hospitalization but did not show sustained improvement of viral suppression.[140] Integration of directly observed ART in methadone maintenance programs (evidence rating BIa)[141] and as a treatment strategy among persons with substance use disorders (evidence rating BIa)[142] and those

who are incarcerated or released to the community (evidence rating CIII)[143] is recommended to enhance adherence and viral suppression.[134]

Missed clinic visits predict clinical events, including mortality,[144] and rapid intervention following a missed visit is recommended (evidence rating AIIa). Personal telephone and interactive short message service (SMS; text) reminders in advance of scheduled appointments and shortly following missed appointments (eg, 24-48 hours) improved retention in HIV medical care across various settings and are recommended (evidence rating AIa).[145,146]

Viral load measurement is not recommended for screening for ART adherence; clinicians should directly screen for adherence, ideally to identify and intervene in ART nonadherence prior to viral rebound. Adherence monitoring using patients' self-reports via validated adherence instruments and pharmacy refill data are recommended (evidence rating AIIa).[134] Self-reports typically overestimate adherence, but degree of self-reported nonadherence predicts virologic failure and even mortality.[147,148] Other interventions that improved ART adherence and some that improved viral suppression are described elsewhere.[134,135]

Active substance use is associated with poor adherence. Opioid substitution therapy for opioid-dependent patients improves retention in care and is recommended (evidence rating AIIa).[149] Depression is associated with poor adherence, and routine screening for depression is recommended (evidence rating AIII).[110,134] Depression treatment improved ART adherence[150] and HIV outcomes[151]; however, 3 US-based randomized clinical trials of antidepressant treatment showed no effect on ART adherence.[152-154] More intensive behavioral interventions integrating depression and adherence counseling showed improvement in both outcomes.[155-157]

Box 6. Recommendations for Engagement in Care and ART Adherence[a]

- Routine opt-out HIV screening is recommended in primary medical care settings and emergency departments and for all pregnant women (evidence rating AIII).
- Systematic monitoring of time to care linkage following initial HIV diagnosis, retention in care, ART adherence, and rates of viral suppression is recommended in all care settings (evidence rating AIIa).
- Brief case management is recommended after HIV diagnosis (evidence rating AIa).
- Rapid intervention following a missed clinic visit is recommended (evidence rating AIIa).
- Integration of directly observed ART in methadone maintenance programs (evidence rating BIa) and as a treatment strategy among persons with substance use disorders (evidence rating BIa) and those who are incarcerated or released to the community (evidence rating CIII) is recommended to enhance adherence and viral suppression.
- Personal telephone and interactive text reminders in advance of scheduled appointments and shortly following missed appointments (eg, 24-48 hours) are recommended (evidence rating AIa).
- Adherence monitoring using patients' self-reports by validated adherence instruments and pharmacy refill data are recommended (evidence rating AIIa).
- Opioid substitution therapy for opioid-dependent patients is recommended (evidence rating AIIa).
- Routine screening for depression is recommended (evidence rating AIII).

Abbreviation: ART, antiretroviral therapy.

[a] See text for essential details and cautions. All recomendations are new or evidence ratings have changed substantially since the 2014 report.

Prevention

Recommendations for prevention of HIV infection are summarized in **Box 7**. Use of ARVs has expanded beyond treatment of HIV infection. ART for pregnant women can eliminate mother-to-child transmission.[158-160] With "treatment as prevention," heterosexual transmission can be prevented if the HIV-infected partner achieves viral suppression.[4,161-163] An increasingly robust observational data set suggests similar benefit for decreasing transmission among men who have sex with men.[5,164] Data are not available for persons who inject drugs, but the assumption is that there would be a similar benefit. In addition, ARVs are effective as PrEP in reducing the risk of HIV acquisition.

Treatment as Prevention

ART is recommended for all HIV-infected individuals with detectable viremia, not only because of individual health benefits but also because of the reduced infectiousness of ART-treated individuals with virologic suppression (evidence rating AIa).

Preexposure Prophylaxis

PrEP is an effective HIV prevention tool that is part of a "prevention package" for HIV-seronegative persons at risk. Detailed sexual, substance use, and medical histories are important for deciding whether to provide PrEP. Individuals who are candidates for PrEP include anyone from a population with an HIV incidence of at least 2% per year (evidence rating AIa) or HIV-seronegative partners of HIV-infected persons who do not have viral suppression. Guidelines for identifying candidates for PrEP have been published.[165-167] Of note, PrEP does not prevent other sexually transmitted infections.

Daily TDF/emtricitabine with high adherence is highly effective for HIV prevention and is the recommended regimen (evidence rating AIa).[168-173] Intermittent, event-driven PrEP was effective in a single study among a highly sexually active population.[174] There is evidence that 4 or more doses of PrEP per week confers protection against HIV infection through anal sex[169,175,176]; in the event-driven study, the average number of doses taken was 4 per week, which may account for the observed success of this strategy. Less than daily dosing may not be effective for vaginal exposures according to pharmacologic modeling data.[177,178] Therefore, daily dosing of TDF/emtricitabine for PrEP is recommended (evidence rating AIa), and there are currently insufficient data to recommend intermittent dosing.

In a single randomized clinical trial of TDF alone in persons who inject drugs, 49% were protected against HIV infection overall but 74% were protected when drug was detected.[179] Data on efficacy of PrEP for transgender individuals are limited.[169,180] Data on drug-drug interactions between PrEP agents and cross-sex hormone therapy and data on PrEP in transgender women do not exist and are needed.

Box 7. Recommendations for Prevention of HIV Infection[a]

- ART is recommended for all HIV-infected individuals with detectable viremia, not only because of individual health benefits but also because of the reduced infectiousness of individuals achieving virologic suppression with ART (evidence rating AIa).
- PrEP should be considered for anyone from a population whose HIV incidence is at least 2% per year (evidence rating AIa) or HIV-seronegative partners of HIV-infected persons who do not have viral suppression.
- Daily (rather than intermittent) TDF/emtricitabine is the recommended PrEP regimen (evidence rating AIa).
- Tenofovir disoproxil fumarate–based PrEP is not recommended for individuals with osteopenia or osteoporosis (evidence rating AIII) or a creatinine clearance rate of less than 60 mL/min (evidence rating AIIa) and should be used with caution in patients with chronic hepatitis B virus infection (evidence rating BIIa).
- Tenofovir alafenamide/emtricitabine is not recommended for PrEP until effectiveness has been demonstrated in clinical trials (evidence rating AIII). Use of non–TDF-containing PrEP or augmentation of TDF/emtricitabine PrEP with other agents is not recommended (evidence rating AIII).
- HIV testing, preferably with a combination antigen-antibody assay (AIII), serum creatinine, and estimated creatinine clearance is recommended prior to initiation of PrEP (evidence rating AIa).
- Oral, rectal, urine, and vaginal sexually transmitted infection screening, including for syphilis, chlamydia, and gonorrhea, is recommended as appropriate, and any sexually transmitted infections should be treated (evidence rating BIII).
- Vaccination against hepatitis A and hepatitis B for those who are not immune and human papillomavirus vaccination are recommended (evidence rating AIII).
- Vaccination is recommended for women aged 13 to 26 years and for men aged 13 to 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Men aged 22 to 26 years may be vaccinated (evidence rating AIa).
- Follow-up at intervals of no longer than every 3 months is recommended to allow for HIV testing (evidence rating AIII) and sexually transmitted infection screening (evidence rating BIIb).
- Creatinine assessment may be performed at least every 6 months (evidence rating AIII) and perhaps more frequently for some patients (eg, aged >50 years, taking hypertension or diabetes medications, or with estimated glomerular filtration rates at threshold) (evidence rating CIII).
- Ongoing discussions about adherence are recommended, especially in the absence of proven PrEP adherence interventions (evidence rating CIII).
- Patients taking PrEP who have suspected HIV infection, on clinical grounds or while awaiting HIV RNA confirmation of equivocal screening test results, should have a boosted protease inhibitor (ie, boosted darunavir) and and/or dolutegravir added to TDF/emtricitabine pending HIV RNA and resistance testing results (evidence rating AIII).
- Postexposure prophylaxis is recommended as soon as possible after exposure without waiting for confirmation of HIV serostatus of the source patient or results of HIV RNA or resistance testing (evidence rating AIII).
- Tenofovir disoproxil fumarate/emtricitabine plus twice-daily raltegravir or once-daily dolutegravir is recommended by the Centers for Disease Control and Prevention for postexposure prophylaxis; TDF/emtricitabine with cobicistat- or ritonavir-boosted darunavir or TDF/emtricitabine/cobicistat/elvitegravir are reasonable regimens (evidence rating AIIb).
- Postexposure prophylaxis regimens should be continued for 28 days, and HIV serostatus should be reassessed at 4 to 6 weeks, 3 months, and 6 months after exposure (evidence rating AIIb); shorter follow-up (eg, 3 or 4 months) may be possible with a fourth-generation assay.

Abbreviations: ART, antiretroviral therapy; PrEP, preexposure prophylaxis; TDF, tenofovir disoproxil fumarate.

[a] See text for essential details and cautions. All recommendations are new or evidence ratings have changed substantially since the 2014 report. Components separated with a slash (/) indicate that they are available as coformulations.

Because of the TDF component, TDF-based PrEP is not recommended for those with osteopenia or osteoporosis (evidence rating AIII) or a creatinine clearance rate of less than 60 mL/min (evidence rating AIIa) and should be used with caution in those with HBV coinfection (out of concern for flares of hepatitis or hepatic decompensation on cessation of treatment, particularly among patients with cirrhosis) (evidence rating BIIa).

Approximately 9%[168] to 14%[175] of individuals receiving PrEP experience gastrointestinal adverse effects, which are often self-limited. Glomerular dysfunction with decreases in creatinine clearance rate may occur[181,182] and to date have been reversible with discontinuation. Rechallenge with the PrEP regimen is often possible.[183,184] Tenofovir disoproxil fumarate–based PrEP has been associated with a 1% to 1.5% loss of bone mineral density at 48 weeks at the hip and spine,[185-187] with return to baseline on discontinuation of PrEP.[188] Individuals at high risk of osteopenia or osteoporosis should carefully weigh risks and benefits of PrEP.

HIV testing, preferably with a combination antigen-antibody assay (evidence rating AIII), serum creatinine, estimated creatinine clearance, and hepatitis B surface antigen must be performed prior to initiation of PrEP (evidence rating AIa). For high-incidence populations, especially those with a history of recent exposure, an HIV RNA assay may be helpful in excluding acute HIV infection prior to PrEP. Oral, rectal, urine, and vaginal sexually transmitted infection screening, including serologic testing for syphilis and nucleic acid amplification testing for chlamydia and gonorrhea, is recommended as appropriate, and any sexually transmitted infections should be treated (evidence rating BIII). Vaccination against hepatitis A and hepatitis B viruses is recommended for those who are not immune (evidence rating AIII). Vaccination is recommended for women aged 13 to 26 years and for men aged 13 to 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Men aged 22 to 26 years may be vaccinated (evidence rating AIa).[189] Women should be screened for pregnancy.

Intervals of follow-up should be no longer than every 3 months to allow for HIV testing (by antigen-antibody assay unless symptoms or signs of acute HIV infection are present, in which case HIV

RNA testing should be ordered) (evidence rating AIII) and sexually transmitted infection screening (evidence rating BIIb).[190] Creatinine assessment may be performed at least every 6 months (evidence rating AIII) and perhaps more frequently for some patients (eg, those aged >50 years, taking hypertension or diabetes medications, or with eGFRs at threshold)[181,191] (evidence rating CIII). Adherence is crucial to the success of PrEP, and ongoing discussions about adherence are important, especially in the absence of proven PrEP adherence interventions (evidence rating CIII).

Any positive HIV screening test result for a patient receiving PrEP should prompt immediate confirmatory testing for HIV RNA and genotype testing if confirmed. Patients using PrEP who have suspected HIV infection, on clinical grounds or while awaiting HIV RNA confirmation of equivocal screening test results, should have a boosted PI (ie, boosted darunavir) and/or dolutegravir added to TDF/emtricitabine pending HIV RNA and resistance testing results (evidence rating AIII). Resistance has been observed rarely and most commonly (although not universally) when PrEP with TDF/emtricitabine is initiated during occult acute HIV infection and most commonly with M184V/I alone. Transmission of multiclass-resistant HIV despite daily PrEP use was recently reported in a gay man in North America.[192]

Currently, there are no human data to support the efficacy of other oral HIV ARVs for PrEP. Despite an attractive safety profile and a promising result in an animal study,[193] tenofovir diphosphate levels in genital compartment tissues were low following administration of a single dose of TAF.[194] Tenofovir alafenamide/emtricitabine is not recommended for PrEP until effectiveness has been demonstrated in clinical trials (evidence rating AIII). Use of non–TDF-containing PrEP or augmentation of TDF/emtricitabine PrEP with other agents is not recommended (evidence rating AIII).

Postexposure Prophylaxis

PEP is an emergency intervention designed to abort HIV acquisition in the event of occupational (ie, needlestick or mucous membrane splash) or nonoccupational (ie, sexual or injecting drug use) exposure to HIV-infected blood or potentially infectious bodily fluids. A case-control study estimated an efficacy rate of 81% for zidovudine monoprophylaxis.[167,195] Efficacy is likely higher for combination PEP, but no data exist.[195] PEP is recommended as soon as possible without waiting for confirmation of HIV serostatus of the source patient or results of HIV RNA or resistance testing (evidence rating AIII). The majority of guidelines recommend PEP initiation only within 72 hours of exposure.[196] Baseline assessments should include HIV antibody testing (ideally, a combination antibody/antigen test), sexually transmitted infection testing, pregnancy testing for women of childbearing potential, and hepatitis B and C serologies. The Centers for Disease Control and Prevention recommend TDF/emtricitabine plus twice-daily raltegravir or once-daily dolutegravir[196]; TDF/emtricitabine with boosted darunavir or TDF/emtricitabine/cobicistat/elvitegravir are reasonable alternatives (evidence rating AIIb). PEP should be continued for 28 days, and HIV serostatus should be reassessed 4 weeks to 6 weeks, 3 months, and 6 months after exposure (evidence rating AIIb), although shorter serologic follow-up (eg, at 3 or 4 months) may be possible if using a fourth-generation assay. Persons who repeatedly seek PEP should be considered for PrEP, as daily PrEP may be more protective than repeated episodes of PEP.[165]

Future Directions

Up to 96% of patients who remain in care and receive ART have undetectable plasma HIV RNA levels.[22-26] Newer therapies must be potent, simple, safe, and tolerable to be competitive or fulfill a specific niche, such as activity against multidrug-resistant variants or availability as long-acting formulations.

Long-acting ART may allow patients who have difficulty with daily oral therapy to maintain suppression, allow for directly observed therapy in clinical or nontraditional settings, and provide treatment during periods when oral therapy is difficult (eg, surgery, travel, mental illness, or transitions from hospitalization to outpatient care). With a combination of a nanoformulated NNRTI (long-acting rilpivirine) and an InSTI (injectable cabotegravir), virologic suppression was maintained for 32 weeks when given intramuscularly once every 4 weeks or 8 weeks.[197] Other long-acting therapies being evaluated include implantable sustained-release platforms, nanoparticles, viral vector delivery, monoclonal antibodies, and longer-acting oral therapy.[198,199] Long-acting ART has the potential to reduce the need for daily adherence to oral therapy, but suboptimal adherence to long-acting ART may also have adverse consequences, as delayed or missed treatment could mean prolonged periods with subtherapeutic ART levels, increasing the risk of suboptimal drug concentrations. Therefore, patients at high risk of suboptimal adherence may require comprehensive treatment strategies to avoid delayed or missed doses. Furthermore, what makes therapies long-acting (eg, peptides in viral vectors, depot formulations, pharmacologic enhancers, etc) may have their own drug interactions or long-term toxic effects, and further evaluation is needed.

Injectable and other long-acting preparations for PrEP are currently in clinical development, including long-acting rilpivirine and long-acting cabotegravir[200] and a vaginal ring containing the NNRTI dapivirine, which had a 27% to 30% efficacy in preventing HIV infection among women in sub-Saharan Africa.[201,202]

Another investigational approach for both HIV treatment and prevention is therapies using broadly neutralizing antibodies, which may offer a new opportunity to clear replicating virus,[203,204] clear infected cells,[205] and provide passive immunization to protect at-risk individuals.[206] The hurdles for these therapies include the requirement for parenteral dosing, potential development of anti-idiotypic antibodies, and potential resistance to broadly neutralizing antibodies in infected patients.

Ultimately, if a cure for HIV infection could be developed, the consequences of the infection (eg, chronic inflammation and immune damage) and the need for ART would be eliminated. An ideal cure would also eliminate the need for routine monitoring and the stigma of having been infected with HIV. This target is a high bar. There are 2 potential types of cure: (1) a functional cure, in which an infected person controls infection without therapy and without the consequences of HIV-related immune activation or inflammation and (2) an eradication cure, in which all replication-competent virus is purged from an infected individual. The current search for a cure is both aspirational and necessary to build the foundation of knowledge to design and test cure strategies. Current strategies include reactivating latent virus and purging it from reservoirs (ie, "shock and kill"),[207] gene therapy (knocking in protective genes such as fusion peptide or silencing

RNA[208-210] or knocking out susceptible genes such as *CCR5*[211] or the provirus), and immune enhancement (eg, therapeutic vaccines and immune checkpoint modulators).[212] Similar to ART, a successful cure strategy may require more than 1 agent delivered simultaneously or in a series. To gain widespread use, functional or eradication cure strategies must have limited risk, given the safety and effectiveness of current ART.

In addition, to further maximize the enormous potential benefit of ART on the global HIV epidemic, newer, less toxic drugs must be made available in all countries; health care systems must be strengthened, including increased focus on early diagnosis and timely linkage to and retention in care; and routine viral load monitoring must be implemented to identify treatment failures early and minimize the emergence of resistance. Widespread implementation of early diagnosis and treatment requires a global effort to reduce stigma and discrimination and to ensure that HIV-infected individuals seek help without restrictions.

Conclusions

Antiretroviral agents remain the cornerstone of HIV treatment and prevention. All HIV-infected individuals with detectable plasma virus should receive treatment, with recommended initial regimens consisting of an InSTI plus 2 NRTIs. PrEP should be considered as part of an HIV prevention strategy for at-risk individuals. When used effectively, currently available ARVs can sustain HIV suppression and can prevent new HIV infection. With these treatment regimens, survival rates among HIV-infected adults who are retained in care can approach those of uninfected adults.

ARTICLE INFORMATION

Author Affiliations: University Hospital Zurich and Institute of Medical Virology, University of Zurich, Zurich, Switzerland (Günthard); University of Alabama at Birmingham, Birmingham (Saag, Mugavero); University of California San Diego School of Medicine, San Diego (Benson); Emory University Rollins School of Public Health and School of Medicine, Atlanta, Georgia (del Rio); University of North Carolina at Chapel Hill School of Medicine, Chapel Hill (Eron); Southwest CARE Center, Santa Fe, New Mexico (Gallant); Alfred Hospital and Monash University, Melbourne, Australia (Hoy); Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Sax); AIDS Research Consortium of Atlanta, Atlanta, Georgia (Thompson); Massachusetts General Hospital and Harvard Medical School, Boston (Gandhi); University of California Los Angeles (Landovitz); University of California San Diego, La Jolla (Smith); International Antiviral Society–USA, San Francisco, California (Jacobsen); University of California San Francisco (Volberding).

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Günthard, Saag, Benson, Del Rio, Eron, Gallant, Hoy, Mugavero, Sax, Thompson, Gandhi, Landovitz, Smith, Volberding.
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